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Neurobehavioral Consequences of Postnatal Exposure to Toxicants

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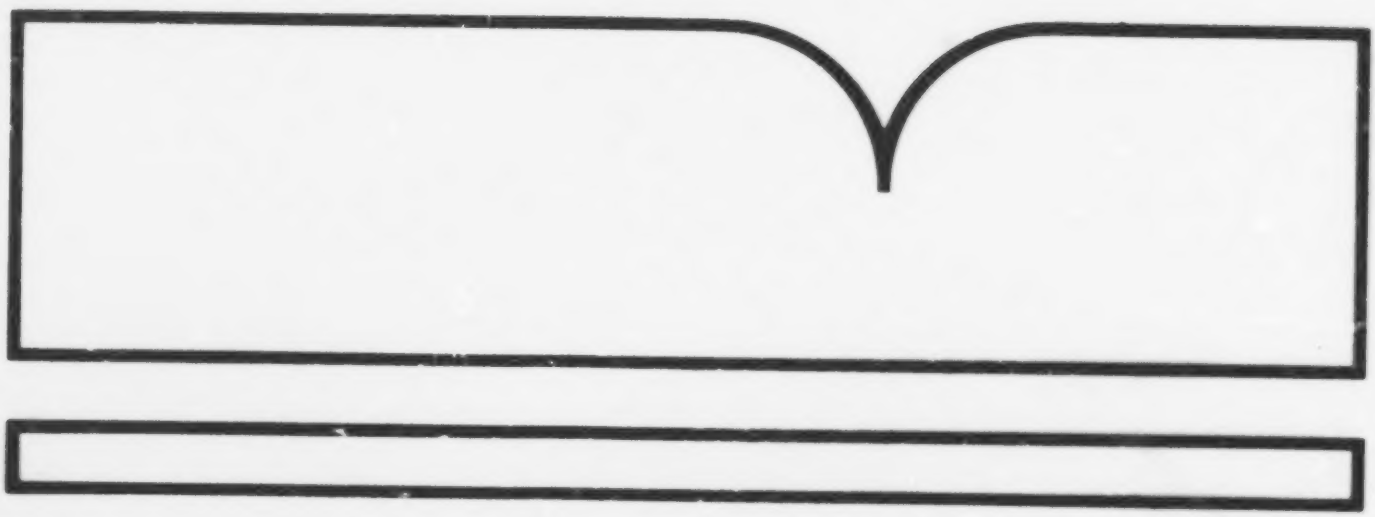

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NEUROBEHAVIORAL CONSEQUENCES OF POSTNATAL EXPOSURE TO TOXICANTS

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16. ABSTRACT

Behavioral teratology is the study of the functional consequences of exposure to toxicants during the period of nervous system development. These agents include therapeutic drugs, food additives, hormones, alcohol, drugs of abuse, heavy methals, pesticides, solvents, and x-irradiation. "Birth defects of the mind" (Kolata, 1978) have become a matter of public concern as more becomes known about adverse effects of chemicals in our environment (Spyker, 1975) as well as adverse effects of drugs to which pregnant women and infants are exposed (Hutchings, 1978; Barlow, 1982).

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Overview

Behavioral teratology is the study of the functional consequences of exposure to toxicants during the period of nervous system development. These agents include therapeutic drugs, food additives, hormones, alcohol, drugs of abuse, heavy metals, pesticides, solvents, and X-irradiation. "Birth defects of the mind" (Kolata, 1978) have become a matter of public concern as more becomes known about adverse effects of chemicals in our environment (Spyker, 1975) as well as adverse effects of drugs to which pregnant women and infants are exposed (Hutchings, 1978; Barlow, 1982). Table 1 indicates organizational principles (Vorhees and Butcher, 1982) derived from teratology, neurobiology and psychology which are applicable to the study of behavioral teratology as a scientific discipline.

The prolonged period of nervous system development, which begins early in gestation and extends into postnatal life, contributes to the vulnerability of the developing brain. Although teratological studies have focussed on prenatal exposure to toxicants, later stages of nervous system development are also vulnerable to toxic insult. Exposure during this later period, when the complex circuitry of the brain is being established, may produce subtle alterations in brain development which are most easily detected by behavioral assays (Davison and Dobbing, 1966).

For assessing risk to the human fetus and infant from exposure to potential neurotoxicants during later stages of brain development, i.e., in the perinatal period, a comparable stage of brain growth in an animal model must be evaluated. In the rodent, a comparable period occurs postnatally. Donaldson (1908) described the relationship between the growth of the brain in the albino rat and man, and concluded that the brain of the rat on PND 5-6 was equivalent to that of the human at birth. Subsequent comparisons of brain growth in several species (Dobbing and Sands, 1979) confirmed that the timing of the brain "growth spurt" in the rat and man was comparable (Figure 1): the first week of postnatal life in the rat is equivalent to the stage of development of the human brain at the end of the third trimester of pregnancy. Therefore, early postnatal exposure in the rodent encompasses a time span equivalent to perinatal exposure in the human.

Behavioral evaluation in rats following postnatal exposure to potential neurotoxicants can be a useful strategy for assessing the functional consequences of neurotoxic insult during later stages of brain development. The objectives of this review are: 1) to present the major events of postnatal brain development in the rat, 2) to present some behavioral approaches for assessing postnatal insult, 3) to indicate how postnatal disruption of brain development by X-irradiation or by alterations in the

hormonal milieu produces behavioral dysfunction, and 4) to present experimental data on the behavioral effects of postnatal exposure to heavy metals. Animal models of postnatal exposure to metals are particularly relevant given the potential for direct exposure to human infants by transferral through the mother's milk, the use of contaminated water in the preparation of infant formula, and the contamination of either food or containers used for infant and junior food (Schmidt and Hildebrandt, 1983). Experimental data on the behavioral effects of heavy metal exposure will include recent research, including published abstracts, whereas literature reviews will be cited as sources for much of the background material presented in this chapter.

Postnatal Development of the Nervous System

In contrast to the recent origin of behavioral teratology as a scientific discipline, elegant studies by Ramon y Cajal and by other early neurobiologists in the late nineteenth century established many fundamental principles of brain organization and development. Following induction of the neural plate, the stages of neurogenesis are: proliferation of cells, migration of cells, aggregation of cells into brain regions, differentiation of immature neurons, formation of synaptic connections, selective cell death, and the elimination and stabilization of synapses (Cowan, 1979; see also Jacobson, 1978; Suzuki, 1980). The

timing of these neural events differs by species but the sequence of development does not.

In the rat, even the early stage of neurogenesis, the proliferation of neurons, continues postnatally. Allen (1912) reported evidence of mitosis in the cortex and cerebellum of the rat during the first postnatal week. Although the majority of proliferating cells in the postnatal brain are glia, later studies demonstrated that granule cells in the olfactory bulb, cerebellum and hippocampus continue to proliferate in postnatal life (Altman, 1970). Because of this ongoing neurogenesis, X-irradiation and agents which affect dividing cells can disrupt postnatal development. In humans, the time span for nervous system development is longer than for the rat, yet proliferation of neurons still occurs in bursts separated by periods of inactivity (Rodier, 1980). Therefore, even acute insults can have profound consequences in both species during episodes of rapid growth.

Examples of postnatal processes which are susceptible to insult during this period of rapid development in the rat are as follows:

Neuronogenesis In the hippocampus, 80% of the granule cells are formed postnatally, and during the peak of proliferation (PND 5-PND 8) at least 50,000 neurons are generated each day (Schlessinger et al., 1975).

Synaptogenesis Less than 1% of the adult number of synapses

are present in the dentate gyrus of the hippocampus on PND 4, but the number doubles every day between PND 4 and PND 11 (Crain et al., 1973).

Myelinogenesis During the peak period of myelination (PND 20), each oligodendrocyte synthesizes 3 times its own weight of myelin each day (Norton and Poduslo, 1973).

As illustrated by these examples, the brain growth spurt encompasses many developmental events, which occur at different times in different brain regions. The question arises: when is brain development complete? Many neuroanatomical and neurochemical parameters of development attain adult levels in the postweaning period (Ford, 1973); others such as deposition of myelin (Norton and Poduslo, 1973) and proliferation of granule cells in the hippocampus (Bayer et al., 1982) continue to occur well into adult life. These later "developmental" phenomena may be particularly sensitive to toxic insult. For example, brain growth in juvenile rats is reduced by administration of phenobarbital from PND 25-39 (Diaz, 1983), indicating that the developmental neurotoxicity of barbiturates (Reinisch and Sanders, 1982; Fishman and Yanai, 1983) continues beyond the prenatal and immediate postnatal period.

Postnatal Development of Behavior

Although the development of behavior can be studied prenatally (behavioral embryology), behavioral assessment usually encompasses the period from birth to maturity or old

age. Many behavioral test strategies and test batteries have been recommended for assessment of animals exposed to toxicants during development (Butcher, 1976; Grant, 1976; Rodier, 1978; Buelke-Sam and Kimmel, 1979; Zbinden, 1981; Vorhees and Butcher, 1982). Most recommendations agree that multiple functions should be assessed, since it is unlikely that any single behavior will be disrupted by all toxicants. Two promising approaches to assessing effects of postnatal toxicant exposure are the emergence of behavioral function in pups and social behavior in juveniles and adults.

Behaviors which are specific to development, such as homing, suckling and distress vocalizations can be indicators of acute toxicity and also predictors of impaired development (Adams and Buelke-Sam, 1981; Zbinden, 1981). In addition, these species-specific or instinctive behaviors have allowed developmental pyschopharmacologists to study the role of neurotransmitter systems in regulating behavior at a very early age. This is particularly true for suckling (Caza and Spear, 1982; Spear and Ristine, 1982). Thus these behaviors can be informative because they provide for the study of mechanisms as well as for the detection of toxicity.

Preweaning evaluation of sensory, cognitive and motor function can be used to assess delays in development, and can allow comparison with deficits seen after maturity. For reflexes such as the startle response, not only the presence

or absence of a reflex can be assessed, but also the number of responses, amplitude, latency, habituation, sensitization, and prepulse inhibition (e.g., Parisi and Ison, 1979) which may be more sensitive indicators of toxicity. Preweaning tests of passive avoidance, taste aversion, runway performance etc. (see Spear and Campbell, 1978) have been adapted to the motor and sensory capacities of the developing animal. A peak in preweaning locomotor activity which occurs on PND 15 (Campbell et al. 1969) can be useful for assessing acceleration or retardation of development. Also the daily monitoring of behavior such as emergence of pups from a nest box (Norton et al., 1975) can be informative for assessing the development of motor activity of pups within the social unit of dam and siblings.

Social behavior has been generally ignored in behavioral teratology studies (Buelke-Sam and Kimmel, 1979), and most laboratories which do investigate social behavior use a criterion of mating success or fertility as the endpoint. Sexually dimorphic behaviors, which depend on the hormonal environment in perinatal life, offer a different perspective in behavior teratology (Balazs, 1981; Larsson and Hard, 1982) since alterations in behavior produced by toxicant exposure can reflect damage to the developing neuroendocrine system. Social interactions at different stages of the lifespan can be assessed in prepubertal play behavior and adult mating behavior.

Juvenile rats are often described as active, playful and "inattentive" (Altman et al., 1973) when compared to either neonates or adults. On simple learning tasks, they may perform better than adults, while performance of juveniles can be impaired on more complex tasks (Spear and Brake, 1983). Experimental studies have confirmed observational reports of playfulness in juvenile rats and described the ontogeny of this behavior (see Panksepp, 1981) which is characterized by vigorous chasing, pouncing and wrestling. The presence or absence of androgen (Olioff and Stewart, 1978; Meaney and Stewart, 1981), brain lesions (Meaney et al., 1981; Beatty and Costello, 1983) and psychotropic drugs (Beatty et al., 1982; Thor and Holloway, 1983) can modify the intensity of juvenile play behavior.

Social behaviors in adults which are related to reproductive function include dominance, aggression, mating behavior and parental behavior. These behaviors in the postpubertal rat depend not only on the action of gonadal hormones during development, as does play behavior, but also on the action of gonadal hormones in adulthood. The temporal patterning and frequency of these behaviors, such as male sexual behavior, can be altered by hormone withdrawal or replacement, by specific brain lesions and by alterations of neurotransmitter functioning (see Sachs and Barfield, 1976). Tests which evaluate precopulatory behaviors such as approach and contact directed towards a

partner (Eliasson and Meyerson, 1975, 1981) may indicate behavioral alterations which precede reproductive failure.

Maternal behavior is of interest in behavioral teratology from another perspective, i.e., the interactions between the dam, pups and littermates following toxicant exposure. A continuing concern in behavioral teratology is that these interactions will confound the interpretation of developmental toxicity. Consequently, in prenatal studies, pair-fed dams and cross fostering have been used as control procedures. In postnatal studies, comparisons have been made between litters in which pups were reared with dosed littermates and litters in which pups were reared with littermate controls (Pearson et al., 1980; Booze et al., 1983b; Ruppert et al., 1983a). Also, rearing of pups in an artificial environment (Goldenring et al., 1982) or an enriched environment (Petit and Alfano, 1979) can modify the effects of toxicant exposure. Rather than being considered a confound, the preweaning environment can be considered a source of information on how toxicity can be modulated by nutritional, social, and experiential factors.

Experimental Disruption of Postnatal Development

The study of abnormal development often has been used to elucidate processes involved in normal development. Within behavioral teratology, as in other disciplines, a range of interests are represented. Experiments have focussed on nervous system development, on behavioral

function, on the action of a particular agent, or on the development of animal models of human disorders. Studies of X-irradiation and hormonal imbalances during postnatal development are relevant to behavioral teratology since toxicants themselves can affect postnatal neurogenesis and the developing neuroendocrine system.

X-irradiation

Experiments investigating the effects of ionizing radiation during development have been directed towards several objectives: 1) describing the effects of radiation and analyzing the mechanisms of malformation, 2) using radiation as a technique to produce specific brain damage, 3) using malformed animals to find correlations between developing brain and behavior, and 4) understanding and preventing radiation hazards in humans (Hicks and D'Amato, 1978). Altman and his colleagues have used postnatal X-irradiation of the cerebellum and hippocampus to examine the relationship between abnormal brain development and behavioral function. These studies have described the types of experimental situations in which X-irradiated animals show behavioral deficits.

Focal X-irradiation of the cerebellum beginning on or before PND 4 produced an extensive reduction in the number of granule cells, and severe disturbances of motor coordination and balance (Anderson and Altman, 1972). When X-irradiation began on PND 8 or PND 12, hyperactivity with

only minimal motor impairment was seen (Pellegrino and Altman, 1979). Lynch et al. (1976) described a transition between PND 6 and PND 8 for the severity of motor impairment produced by X-irradiation of the cerebellum. These studies emphasize that the type of damage produced within a given brain area and the behavioral changes which result depend on the timing of the insult during the postnatal period.

Destruction of granule cells of the hippocampus resulted in hyperactivity (Bayer et al., 1973; Peters and Brunner, 1976) and deficits on learning and memory tasks (Bayer et al., 1973; Gazzara and Altman, 1981) which were typical of animals with hippocampal lesions. Learning disabilities in X-irradiated animals were more often seen on tasks which required an animal to inhibit responding, and on tasks which involved more difficult discriminations. The level of task difficulty was also an important factor in detecting motor impairment produced by X-irradiation of the cerebellum, which emphasizes that careful behavioral analysis is often needed to detect even gross brain damage.

Because of the extensive postnatal proliferation of granule cells in the cerebellum and hippocampus, these areas might be generally susceptible to postnatal insult, and motor incoordination, changes in motor activity and altered learning behavior would be anticipated behavioral outcomes. The postnatal effects of chemical neurotoxicants, e.g. methylazoxymethanol (Lai et al., 1978), are consistent with

X-irradiation effects and support the postnatal susceptibility of the cerebellum and hippocampus.

Hormones

Either deficiency or excess of thyroid, adrenal or gonadal hormones in the postnatal period can have pronounced consequences for brain development and behavior. Areas of the brain such as the hippocampus and cerebellum, which are vulnerable to X-irradiation, are also vulnerable to alterations in the postnatal hormonal milieu. Lauder (1983) has summarized evidence that in the hippocampus and cerebellum, cell proliferation, cessation of cell division, formation of neurons, axonal and dendritic growth, neuronal migration and formation of synapses depend on the varying levels of thyroid and corticosteroid hormones in postnatal life. In the hypothalamus, gonadal hormones modify the type of synapse (Raisman and Field, 1973) and the volume of a sexually dimorphic nucleus (Gorski et al., 1977) within the preoptic area. Toxicants can interact with the developing neuroendocrine system to disrupt function at several levels: chlorinated hydrocarbon insecticides have estrogenic properties (Gellert, 1978) and excitatory amino acids produce hypothalamic lesions (Olney, 1980).

Behavioral studies exploring effects of hypothyroidism and hyperthyroidism have placed special emphasis on the preweaning period to assess retardation or acceleration of development. A systematic study of the effects of thyroid

hormone excess and deficiency on development was begun by Eayrs in the 1950's. To determine the critical period for the effects of triiodothyroxine (T3) stimulation (Eayrs, 1964), rat pups were injected either throughout lactation (PND 1-24), or only at the beginning (PND 2-4) or end (PND 14-20) of the preweaning period. Eye opening was accelerated by 4-5 days in pups receiving T3 throughout PND 1-24 or only on PND 2-4. Both groups made more errors than controls on a maze learning task as adults. No deficits in maze learning were seen in animals injected only at the end of the preweaning period. Therefore, in subsequent studies by other investigators which characterized effects of excess thyroid hormones on development (Schapiro, 1968: Schapiro et al., 1970; Davenport and Gonzalez, 1973; Stone and Greenough, 1975; Murphy and Nagy, 1976 a,b; Sjoden and Soderburg, 1976; Kessler and Spear, 1980; Brunjes and Alberts, 1981), pups were injected during this sensitive period between PND 1-5. The general conclusion from these studies, in agreement with the work of Eayrs, is that hyperthyroidism during the first week of postnatal life in both rats and mice accelerates behavioral maturation and development in the preweaning period, but produces performance deficits in adolescents and adults. Hypothyroidism results in hyperactivity and learning deficits (Eayrs and Lishman, 1953; Eayrs and Levine, 1962; Davenport and Dorcey, 1972; Schalock et al., 1979; Strupp

and Levitsky, 1983).

Postnatal life is also a critical period for the action of gonadal hormones on sexual differentiation of the brain and behavior in rats. Table 2 illustrates the effects of perinatal androgen treatment on sexually dimorphic characteristics in females of several species (Goy and McEwen, 1980). There is a striking correspondence between the time of the brain growth spurt in these species (see Figure 1) and the time of maximum effect of gonadal hormones on these sexually dimorphic characteristics. Both periods occur prenatally for the guinea pig, sheep and monkey and postnatally for the rat. Like the brain growth spurt, sexual differentiation is not a single process occurring at a single time in postnatal life. Rather, the production of anovulation, masculinization and/or defeminization depends on the type of hormone, the amount, and the time within this period when it is present (see MacLusky and Naftolin, 1981). In female rats, a single injection of testosterone produces a continuum of effects on ovarian function which are age dependent: anovulatory sterility is produced by dosing on PND 1-4, while a delayed anovulatory syndrome is produced by dosing on PND 5-6 (Gorski, 1968). Male rats castrated on or before PND 5 display high levels of feminine sexual behavior but incomplete masculine sexual behavior when treated with appropriate hormones as adults (Grady et al., 1965).

Sexually dimorphic behaviors which are not directly

related to reproduction may also be influenced by the presence or absence of gonadal hormones in postnatal life. Behaviors for which sex differences have been described in adult rats include motor activity, pain, taste sensitivity, food intake and body weight regulation, learning and retention of certain types of mazes, avoidance responses, taste aversion, and performance on some schedules of reinforcement (see Beatty, 1979). The magnitude of these differences are generally small and are criticallly dependent on test procedures. Therefore, if toxicants affect the contribution of sex differences to these behavioral baselines, this effect might be difficult to detect.

Behavioral Consequences of Postnatal Exposure to Metals

Metals which have been evaluated for behavioral toxicity in animal models following postnatal exposure include cadmium, inorganic lead, triethyl lead, methylmercury, triethyltin and trimethyltin. In general, the toxicity of these metals is characterized by steep dose-response functions. To provide a framework for interpreting behavioral toxicity, dosages which produce mortality and reduce growth have been reported in most studies. In addition, brain weight has been included in most studies to indicate the relationship between dosages producing behavioral dysfunction and overt CNS toxicity. Reductions in brain weight have been reported following

postnatal exposure to cadmium (Rastogi et al., 1977; Wong and Klaassen, 1982), lead (Petit and Alfano, 1979), triethyltin (Reiter et al., 1981), and trimethyltin (Ruppert et al., 1983b). Hippocampal weight was preferentially decreased by inorganic lead (Petit and Alfano, 1979) and the organotins (Ruppert et al., 1983a, b), indicating selective toxicity. Many studies have evaluated behaviors related to neural function in the hippocampus, cerebellum and olfactory system due to the extensive postnatal development in these brain areas.

Cadmium

Cadmium (Cd), which produces limited CNS toxicity in adults (Arvidson, 1981), is neurotoxic to developing animals, producing gross structural damage to the brain following postnatal exposure (Gabbiani et al., 1967; Webster and Valois, 1981; Wong and Klaassen, 1982). Age-related changes have been observed during postnatal life in the profile of neuropathology in both rats (Gabbiani et al., 1967) and mice (Webster and Valois, 1981). Either acute or repeated postnatal exposure produces behavioral toxicity, including alterations in motor activity. Rats exposed to Cd on PND 1-30 were hyperactive in a selective activity meter 24 hr after the last dose (Rastogi et al., 1977), rats exposed to Cd on PND 6-15 were hyperactive in tilt cages on PND 45-46 (Smith et al., 1982), and rats exposed to Cd on PND 4 were hyperactive in figure-eight

mazes on PND 23 (Wong and Klaassen, 1982). However, mice injected on either PND 1 or PND 8 were hypoactive at 8 wk in an open field (Webster and Valois, 1977). This differential effect of Cd on motor activity could be due to a difference in species, activity measuring device, age at testing, or age of exposure. In a recent study, the development of locomotor activity (PND 13-21) was assessed in rat pups receiving Cd on PND 5 (Ruppert and Dean, 1983). Pups were hypoactive in the initial days of testing but gradually became hyperactive. This biphasic effect on activity may be a characteristic of Cd toxicity which contributes to differences between experiments described above.

Preweaning evaluation of Cd toxicity has recently been reported for pups injected on PND 1 (Newland et al., 1983). Fewer Cd-exposed pups suckled from an anesthetized dam (PND 2) or showed a preference for home bedding (PND 7). For pups injected with Cd on PND 6 (Infurna et al., 1982), homing behavior was altered (PND 7) and deficits in passive avoidance retention were seen in adults. These acute effects of Cd on behaviors such as suckling and homing, which are regulated by olfactory cues, may be predictive of later behavioral effects of Cd exposure; Smith et al. (1982) hypothesized that Cd-induced anosmia could account for altered behavior in learning tests.

Inorganic Lead and Triethyl lead

Effects of inorganic lead exposure on the development

of the nervous system in both humans and several animal models have been extensively studied and reviewed (e.g., Bornschein et al., 1980 a,b). A recent synthesis is that behavioral effects of postnatal lead exposure reflect disruption of hippocampal development (Alfano and Petit, 1981; Petit et al., 1983). In Table 3, behavioral deficits seen in lead-exposed rats are compared with deficits produced by hippocampal lesions (Petit et al., 1983). The value of this conceptualization is the neural framework it provides for interpreting lead toxicity, and the stimulus it provides for further research. However, delays in the development of motor activity and deficits in performance of a preweaning learning task have been reported which correspond to delays in metabolic development of the cerebral cortex (Bull et al., 1983), emphasizing that lead toxicity is not restricted to the hippocampus.

Although the majority of studies describing lead toxicity are based on long-term exposures intended to mimic chronic exposure in children, a few studies have compared the effects of acute and chronic exposure. For example, lithium-induced polydipsia was augmented following chronic lead exposure from PND 3-30 (Mailman et al., 1978). Control animals increased their fluid intake in response to an injection of lithium, and this polydipsic response was augmented in lead-exposed rats. This facilitation has been attributed to an alteration of central catecholaminergic

functioning (Mailman et al., 1978), or to damage within the septal area or hippocampus (Dantzer, 1980). To determine the critical age for this effect, Mailman et al. (1982) intubated rat pups with lead acetate at different times during the preweaning period. A single dosage of 200 mg/kg on either PND 5 or PND 15 produced an increase in lithium-induced polydipsia similar to that produced by daily dosing from PND 3-30. Thus, acute exposure to inorganic lead can be toxic during development.

Triethyl lead (TEL) can also be neurotoxic following a single postnatal exposure. Booze et al. (1983a) assessed preweaning and juvenile behavior in rat pups exposed to TEL on PND 5. Preweaning testing indicated impaired olfactory discrimination (PND 7), fewer pups attaching to a nipple (PND 9), and the presence of tremor (PND 10). Juvenile testing (PND 20-29) indicated a decreased number of responses to a startle stimulus, hypoactivity in male pups, and alterations in affective behavior on passive avoidance retention trials. Long-term evaluation of TEL-exposed pups revealed hyperreactivity on several behavioral tests and cell loss in area CA3 of the hippocampus (Booze et al., 1983c), indicating that postnatal exposure to TEL, like inorganic lead, produces hippocampal dysfunction.

Methylmercury

Methylmercury (MM) intoxication in human populations resulting from poisonings in Japan and Iraq indicated that

gestational exposure disrupted nervous system development more severely than lactational exposure. Therefore, the majority of animal studies describing neurobehavioral sequelae of MM poisoning have used prenatal exposures (see Reuhl and Chang, 1979).

To differentiate between the effects of gestational and lactational exposure to MM, Spyker and Spyker (1977) injected dams with MM on either day 7, 9 or 12 of gestation, and then cross-fostered pups to produce exposure: 1) both prenatally and postnatally, 2) prenatally only, 3) postnatally only, and 4) no exposure. Effects of prenatal exposure to MM on pup survival and growth were twice as large as postnatal effects in cross-fostered pups and were greatest late in organogenesis. This study provides a valuable contribution in explicitly testing for carryover effects of prenatal exposure which could be due to persistence of MM, alterations in maternal behavior etc. However, this experiment does not address the question of direct effects of postnatal exposure to pups.

Zenick (1974) used a water escape T-maze to test groups of rats which had received either gestational, lactational or postweaning exposure to MM. Learning deficits were found following gestational exposure (via the maternal water supply), or postweaning exposure (directly to pups). No deficits were found following postnatal exposure via the dams' milk (PND 1-21). A single dose of mercury to pups on

PND 15 or 21 also produced no changes in discrimination learning or open-field behavior (Post et al., 1973).

When younger pups were exposed directly to MM by intubation or injection, both the morphological (Sager et al., 1982) and biochemical (Taylor and DiStefano, 1976; Bartolome et al., 1982 a,b) development of the nervous system was disrupted. For example, a single injection of 8 mg/kg MM in mice on PND 2 produced neuropathological changes in the cerebellum 24 hr after dosing (Sager et al., 1982). Therefore, behavioral effects of postnatal exposure to MM, especially on behaviors which are sensitive to cerebellar insult, deserve further consideration.

Organotins

Triethyltin (TET) and trimethyltin (TMT) both produce persistent behavioral toxicity when administered to developing animals either on PND 5 or throughout the preweaning period (PND 3-30). Although the behavioral toxicity produced by TET and TMT in adults is dissimilar (Reiter and Ruppert, 1984), there are similarities in the behavioral toxicity produced by these organotins in developing animals. Behavioral consequences of exposure to TET on PND 5 have been most extensively investigated (Harry and Tilson, 1981, 1982; Reiter et al., 1981; Ruppert et al., 1983a; Miller, 1984).

Pups exposed to TET on PND 5 demonstrated motor incoordination, hypoactivity and a learning deficit in the

preweaning period. The ability of pups to descend a rope suspended above the home cage was impaired in pups exposed to TET (Reiter et al., 1981). This deficit in motor coordination may represent cerebellar dysfunction, since cerebellar weight was decreased following TET exposure, and postnatal X-irradiation of the cerebellum also produces deficits in rope descent (Anderson and Altman, 1972). Motor activity was decreased in two preweaning tests, homing orientation and residential activity in a figure-eight maze (Reiter et al., 1981). Both tests provide olfactory and other sensory cues from the litter which have been shown to modulate the activity of rat pups; open-field testing of pups in the absence of these cues did not detect differences in activity. Miller (1984) reported decreased activity in TET-exposed pups tested over home-cage bedding, but not in the absence of bedding. Therefore, this developmental hypoactivity may reflect hypoarousal to olfactory cues. TET-exposed pups required more trials to acquire an alleyway task in which access to home-cage litter and littermates was the reinforcer (Miller, 1984), which also suggests an altered response to olfactory and other cues from the nest.

Postweaning evaluation of animals exposed to TET on PND 5 demonstrated that behavioral deficits were persistent. Hyperactivity (Harry and Tilson, 1981; Reiter et al., 1981; Ruppert et al., 1983a) and decreased startle responsiveness (Harry and Tilson, 1981; Ruppert et al., 1983a) were found

in TET-exposed animals tested as adults; in figure-eight mazes, hyperactivity persisted beyond 200 days of age (Reiter et al., 1981). Harry and Tilson (1982) have shown that stereotypy induced by apomorphine was altered in animals exposed to TET on PND 5, suggesting a persistent functional change in dopaminergic transmission in these animals as adults. Unlike the effects of adult exposure to TET, developmental exposure did not produce neuromuscular impairment in preweaning tests (Reiter et al., 1981), or in grip strength and negative geotaxis tested on PND 21, 28, 60 or 90 (Harry and Tilson, 1981).

Since TET is neurotoxic when injected on PND 5, the toxicity of a single exposure to TET was compared at several ages during the brain growth spurt in early postnatal life (Ruppert et al., 1984). Impaired ability to descend a rope, adult hyperactivity, and decreased brain weight resulted from TET exposure on PND 5, but not from exposure on PND 1, 10 or 15. Figure 2 illustrates motor activity in figure-eight mazes as a function of age at exposure and age at testing. These data demonstrate a differential sensitivity to TET during early postnatal life with maximum susceptibility on PND 5. TET did produce acute toxicity at other exposure ages as indicated by reduced preweaning growth, and persistent toxicity as indicated by deficits in mating behavior in adult males.

TMT is a structurally-related trialkyltin compound

which is also neurotoxic in adults. Ruppert et al. (1983b) evaluated the neurobehavioral toxicity of TMT following exposure on PND 5, and compared these findings with the behavioral toxicity of TET following exposure on PND 5. Impairment of pups' ability to descend a rope, decreased startle response and adult hyperactivity were found. Acquisition deficits in a preweaning learning task and changes in locomotor activity in the presence of home-cage bedding (Miller and O'Callaghan, 1983) were also similar to those produced by TET on PND 5. However, there are qualitative differences which distinguish the developmental toxicity of these organotins. For example, the spatial distribution of motor activity in figure-eight mazes was altered by TET but not TMT.

In a chronic dosing model, neuropathological changes produced by TET and TMT were different (Mushak et al., 1982), yet both organotins produced similar signs of poisoning: tremors and convulsions. Performance on a radial-arm maze was not different between animals exposed to TET or TMT on PND 3-29; neither TET nor TMT impaired accuracy once the task was acquired (Miller et al., 1982). This is surprising because hippocampal pathology following exposure to TMT on PND 3-29 is similar to morphological changes in the adult (Bouldin et al., 1981), and accuracy of performance was decreased following adult exposure to TMT (Walsh et al., 1982). The radial-arm maze, which requires

the use of spatial memory (Olton and Samuelson, 1976), provides some interesting comparisons between the developmental toxicity of heavy metals.

Like chronic exposure to TET and TMT, postnatal exposure to inorganic lead increased the number of days required to reach criterion without decreasing the number of correct choices once the task was acquired (Alfano and Petit, 1981). However, exposure to either TET (Miller, 1984) or TMT (Miller and O'Callaghan, 1983) on PND 5 did decrease accuracy of performance in a radial-arm maze. All the above metals disrupt hippocampal development, and lesions of the hippocampus reduce accuracy on this task (Olton et al., 1979). These divergent results underscore the difficulty in defining relationships between damage to specific brain regions and behavioral changes. The hippocampus is not a homogeneous structure; for example, selective lesions of either the CA1 or CA3-4 pyramidal cell fields have different behavioral effects (Jarrard, 1976). Therefore, differential accuracy of performance may be due to subtle differences in hippocampal pathology between metals and between dosing models, or alternatively, to disruption in other brain regions (see Miller, 1984).

Noland et al. (1982) used preweaning learning tasks to assess organotin toxicity in rat pups whose dams received either vehicle, monomethyltin (MMT) or TMT in the drinking water 14 days before mating through weaning. In this dosing

model, unlike other models for assessing organotin toxicity, exposure began pre-conception and continued through lactation; therefore pups were tested during exposure. Pups from dams receiving organotins in the drinking water required more trials both to acquire and extinguish responding in an appetitive learning task. Responding during extinction persisted in pups receiving all dosages of both MMT and TMT, and many animals did not reach extinction within the 15 trial criterion (see Figure 3). Although the toxicity of monomethyltin compounds is considered to be low (LD50=1370 mg/kg), Noland et al. calculated that the total dosage of Sn received by the dams at the lowest dose of MMT was 104.1 mg/kg. Thus, the potential toxicity of monoalkyltins during development may be greater than for adults.

Summary

This review has focussed on assessment of neurobehavioral function following exposure to toxicants during the early postnatal period in rodents. It was argued, and data were presented for heavy metals, that postnatal exposures can be useful for assessing developmental neurotoxicity. Developmental toxicity can be more persistent than adult toxicity, as shown by triethyltin, and metals which are not overtly neurotoxic in adults, such as cadmium and monomethyltin, can be toxic during development. Given these data, animal models of

exposure to potential neurotoxicants during later stages of brain development warrant further emphasis.

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TABLE 1. PRINCIPLES OF BEHAVIORAL TERATOLOGY

Psychoteratogenicity is expressed as delayed behavioral maturation, impaired rates of learning, abnormal activity, impaired adaptation and problem solving, and other indices of compromised behavioral competence.
The type and magnitude of the response is a function of 1) the type of agent administered, 2) the dose of the agent, 3) the stage of development at which the agent acts, 4) the genetic milieu of the target organism, and 5) the environment of the target organism, i.e., maternal and placental metabolic influences before birth and maternal metabolism, behavior and living environs after birth.
Psychoteratogenic agents are those that are CNS teratogens or those that may be classified as psychoactive agents.
Psychoteratogenesis is a manifestation of abnormal development that is demonstrable at doses of the agent at or below which malformations are induced.
The period of susceptibility to psychoteratogenesis is isomorphic with the period of CNS development, and the period of maximum susceptibility corresponds to the period of maximum susceptibility to structural and physiological abnormalities of the CNS.
Not all agents that are capable of producing malformations are psychoteratogens.

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TABLE 2. EFFECTS OF PERINATAL ADMINISTRATION OF ANDROGENS TO FEMALES ON THE DEVELOPMENT OF SEXUALLY DIMORPHIC TRAITS

Species	Critical Period	Dimorphic characteristic*		
		Ovulation	Sexual Behavior Female	Male
Guinea Pig	Prenatal	——	———	++
Sheep	Prenatal	——	——	++
Rhesus	Prenatal	delayed	?	++
Dog	Pre + Postnatal	?	——	++
Rat	Postnatal	————	———	+
Mouse	Postnatal	————	———	++
Hamster	Postnatal	—	—	++++
Ferret	Postnatal	?	0	+++

*Symbols indicate direction and relative ease of obtaining effect: — = defeminization; + = masculinization; 0 = no effect.

From Gerall in Goy and McEwen (1980) with permission

TABLE 3. COMPARISON OF THE EFFECTS OF HIPPOCAMPAL DYSFUNCTION AND POSTNATAL LEAD EXPOSURE IN SEVERAL TESTING SITUATIONS

Behavior Class	Hippocampal Damage	Postnatal Lead Exposure	Similar
Avoidance Behavior			
passive avoidance	impaired	impaired	√
1-way active avoidance	impaired	impaired	√
2-way active avoidance	facilitation	not clear	
Schedule Controlled Behavior			
CRF	no effect	no effect	√
DRL	impaired	impaired	√
extinction	impaired	impaired	√
Maze Learning			
Hebb-Williams maze	impaired	no effect	
eight-arm spatial maze	impaired	impaired	√
Spontaneous Alternation	impaired	impaired	√
Visual Discrimination			
T-maze	impaired	impaired	√
Y-maze	impaired	impaired	√
operant chamber	impaired	impaired	√
reversal	impaired	impaired	√
Locomotor Behavior			
open field	increased	increased	√
running wheel	no effect	no effect	√
small cage	no effect	not clear	

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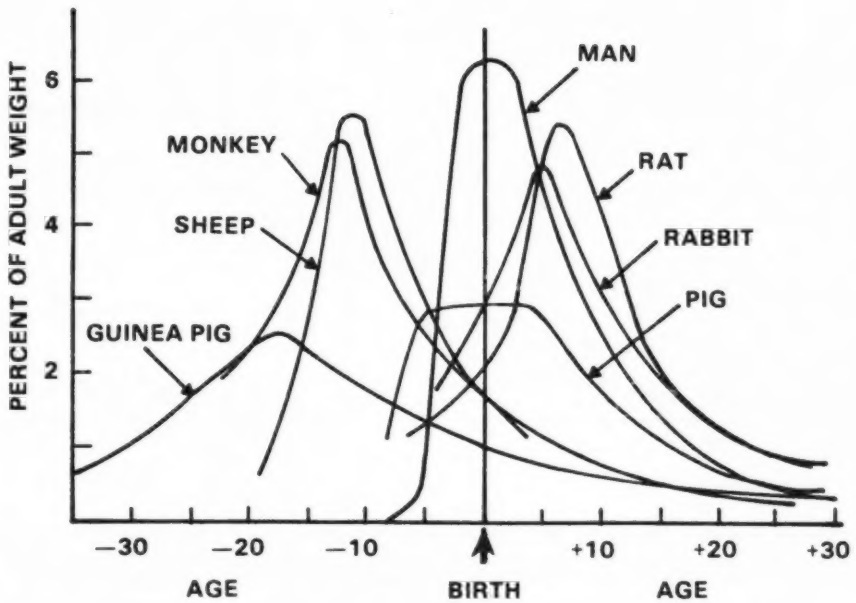

Figure 1. The brain growth spurts of 7 mammalian species expressed as first-order velocity curves of the increase in weight with age. The units of time for each species are as follows: guinea pig [3]: days; rhesus monkey [1]: 4 days; sheep [9]: 5 days; pig [2]: weeks; man [5]: months; rabbit [8]: 2 days; rat [4]: days. Rates are expressed as weight gain as a percentage of adult weight for each unit of time.

FROM DOBBING AND SANDS (1979) WITH PERMISSION

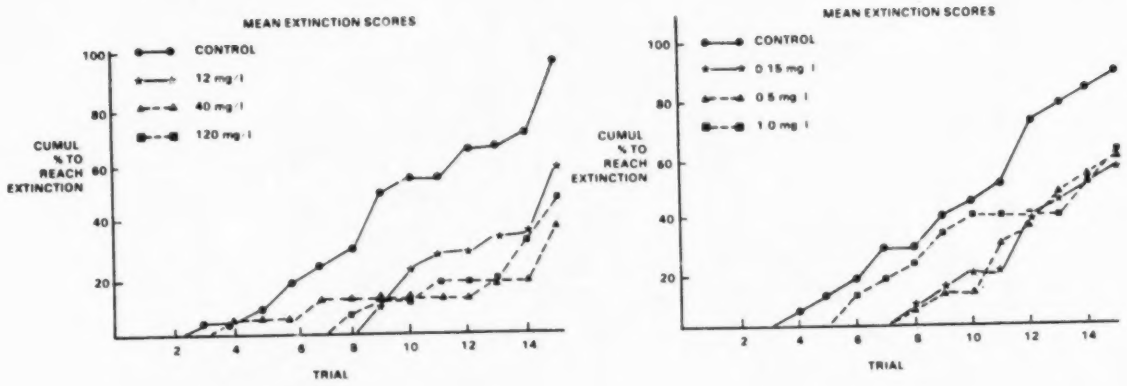

Figure 3 (A). Extinction scores for monomethyltin trichloride exposed groups: cumulative percentage of animals in each group to reach extinction plotted against trial. Sample sizes: control (●)=20; 12 mg/l MMTC (★)=17; 40 mg/l MMTC (▲)=16; 120 mg/l MMTC (■)=15

(B). Extinction scores for trimethyltin chloride exposed groups; cumulative percentage of animals in each dose group to reach extinction plotted against trial. Sample sizes: control (●)=18; 0.15 mg/l TMTC (★)=16; 0.5 mg/l TMTC (▲)=17; 1.0 mg/l TMTC (■)=18.

FROM NOLAND ET AL. (1982) WITH PERMISSION

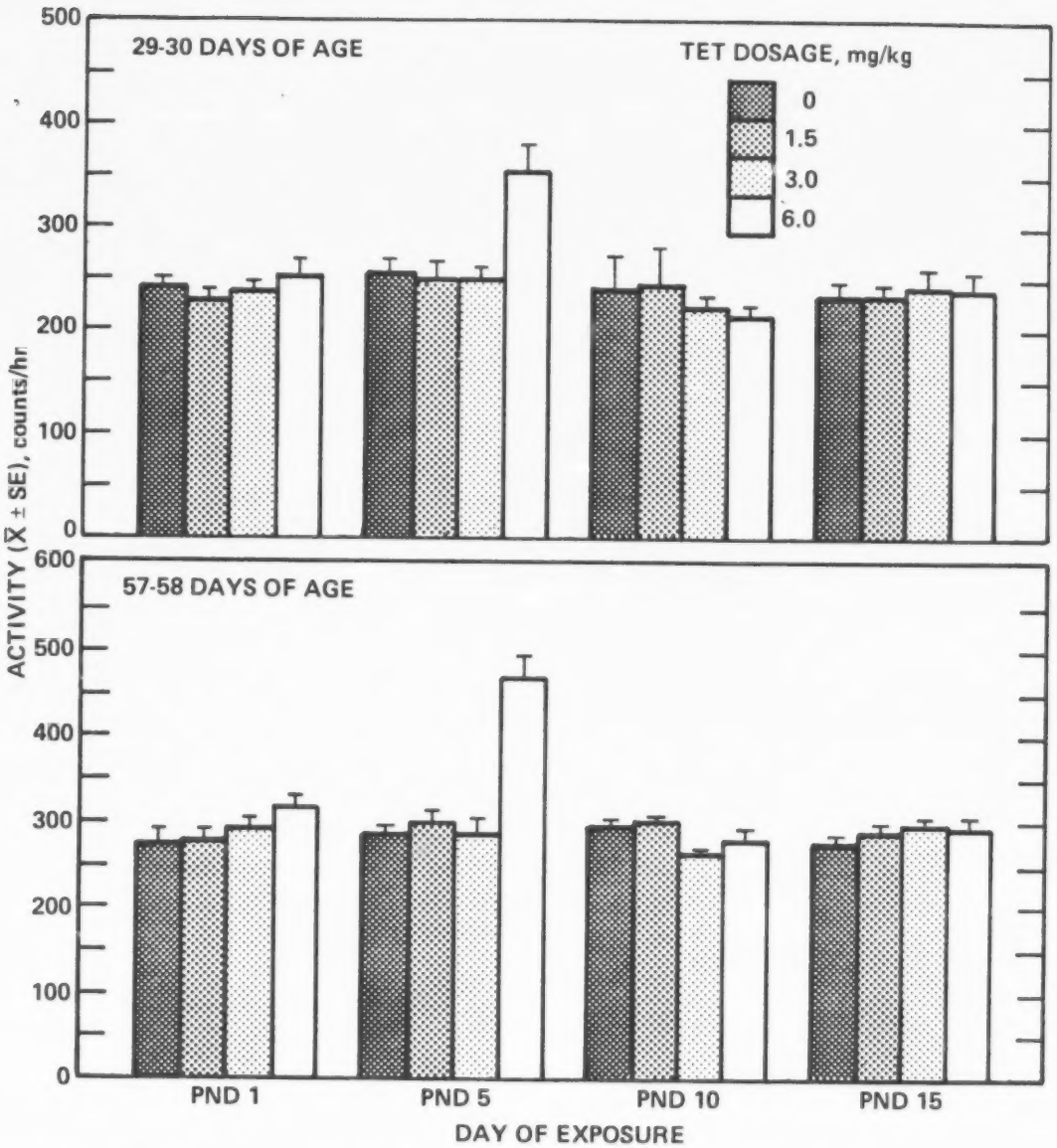

Figure 2. Figure-eight maze activity for control and TET-exposed rats. Data are expressed as photocell interruptions ($\bar{X} \pm SE$) during a 1-hr test session. Exposure to 6 mg/kg TET on PND 5 produced an increase in motor activity at both times of testing.

FROM RUPPERT ET AL. (1984)